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Edwards Angell Palmer & Dodge LLP
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
SWITZER, JULIET CAROLINE	
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1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,097	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12//7/07 and 1/11/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,50,52,53 and 56-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *49,52,53,56,57,64 and 66* is/are allowed.

6)☒ Claim(s) *50,58-63 and 65-87* is/are rejected.

7)☒ Claim(s) *79, 80, 81, and 82* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is written in response to applicant's papers filed 12/7/07 and 1/11/08, including the executed declaration filed 1/11/08.

2. Claims 49, 50, 52, 53, 56, 57, 58-87 are pending and examined herein.

3. This action is FINAL.

4. Claims 49, 52, 53, 56, 57, 64 and 66 are allowed.

5. The previously set forth rejections for lack of enablement have been overcome by amendment and evidentiary showing in the declaration received 1/11/08.

Claim Objections

6. Claims 79, 80, 81, and 82 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 71, 72, 74, and 75. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 50, 67, 68, 69, 77, 84, 85 and 86, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

9. In claims 50, 67, 68, 69, and 77, the limitation that the blood samples "comprise leukocytes which a have not been fractionated into cell types" is new matter. Such a recitation includes, for example, testing a blood sample where the red blood cells and the white blood cells have been separated, and also includes, the testing of whole blood RNA. There is clearly basis for the latter, but not the former.

10. Applicant asserts in the remarks that this claim limitation finds clear support in the specification, including figure 5C which shows standardized fractions of leukocytes. However, these are not leukocytes that have not been fractionated into cell types, as they have clearly been fractionated into cell types. While RNA levels have been determined in each of the fractions, this is not basis for the negative limitation "have not been fractionated into cell types." There is no discussion or example in the specification of the testing of RNA in blood samples which comprise leukocytes which have not been fractionated into cell types. Applicant has attempted to present a claim which excludes a particular process step from a method (that is, fractionating the leukocytes) and then provides basis for the exclusion of the step in a method where the opposite occurred. This is not sufficient basis for the claim limitation because there is nothing in the specification that suggests applicant contemplated the exclusion of a step of fractionating leukocytes into cell types. Therefore, claims 50, 67, 68, 69, and 77, as well as all claims which depend from these claims are rejected for having new matter.

11. In claims 84, 85, and 86, the limitation that recites "wherein said fold-change is 2 or less" represents new matter. The specification does not appear to provide basis for this range, and no basis is identified in the response. This range encompass any small degree of change, while the

specification discloses fold changes of 1.49 and 1.95 in Chagas subjects relative to healthy controls.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 58, 60, 61, 62, 63, 67, 68, 69, 71, 72, 73, 75, 79, 80, and 82, are rejected under 35 U.S.C. 102(a) and 102(b)as being anticipated by William Chittenden, dissertation submitted to the faculty of Virginia Polytechnic Institute and State University, August 2002.

14. These claims are not fully supported under 112 1st paragraph in the instant application nor any of the previously filed applications for at least the reasons discussed in this office action. This reference is applied under 102(a) and 102(b). If applicant establishes support for the claimed invention to a prior application such that the 102(a) and/or 102(b) does not apply the rejection will be withdrawn.

Chittenden teaches quantification and analysis of gene expression in mRNA isolated from whole blood, by isolating cells, precipitating RNA, producing cRNA and hybridization with the probe array HG-U133A, quantification of hybridization and calculation of differential expression. It is an inherent property of this array that it contains probes to CDC14A, and thus, the method taught by Chittenden is a method which uses an oligonucleotides of predetermined sequence which are specific for CDC14A. This chip also inherently has thereupon housekeeping

genes that are used for quantifying expression. Further Chittenden tests individuals with disease and healthy controls (p. 58-59, 62-66). Chittenden does not specifically discuss CDC14A expression, but it would have inherently been detected in the blood of healthy controls by the hybridization and array reading methods. Regarding claims 67, 68, and 69, the blood samples used by Chittenden are considered "whole blood samples" because, all blood samples begin as whole blood samples. The open claim language allows for additional steps to be included in the method.

15. Claims 58, 60, 61, 62, 63, 67, 68, 69, 71, 72, 73, 75, 79, 80, and 82 are rejected under 35 U.S.C. 102(a) as being anticipated by Expression Linked Polymorphism Database, profile for gene CDC14A, 2003.

This rejection is applied in view of the evidence provided in the Expression Linked Polymorphism Database (EXPOLDB), in particular for the entries related to the gene CDC14A. The database is available on the world wide web, and the pages referred to in this rejection were accessed and copied 4/9/2008. All pages of the website that are provided have a copyright date of 2003. Copies of three different linked sections of the site are provided, one nine page summary entitled "Expression Linked Polymorphism Database (EXPOLDB): A resource for linking genome expression with cis modulators of transcription in the Human Genome", one three page entry entitled EXPOL profile for Gene CDC14A, and one which provides graphs of CDC14A expression in blood. The third page is linked to directly in the online interface by following a link from the second page.

The summary teaches that expression variation was examined using oligonucleotide microarrays consisting of probes for genes, and that 5,407 genes were found to be expressed in

blood leukocytes. The summary further teaches that the data will likely be a useful resource for those that are interested in studying natural variations in humans (p. 2 of the summary). Thus, the summary teaches that the expression data provided in the database was obtained by a method of detecting the expression of genes in the blood using oligonucleotides of predetermined sequence to detect expression in the blood. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression, and comparison to these housekeeping genes in an inherent property of methods which use this chip and related analysis. Regarding CDC14A in particular, the EXPOL profile for CDC14A teaches that expression in the blood was detected with a mean expression of 1.66 for 6 arrays (page 2 of the profile), in particular providing also graphs which illustrate this finding. In the example given in the database, the Female subjects are considered "control subjects." Male and female expression is compared in the graph labeled "other individual." There is no disclosure of disease in any of the subjects, and so the evidence suggests that all subjects used in the EXPLODB assays were healthy individuals.

Regarding claims 67, 68, and 69, the blood samples used in the methods taught by EXPLODB are considered "whole blood samples" because, all blood samples begin as whole blood samples. The open claim language allows for additional steps to be included in the method.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 59, 60, 61, 62, 63 67, 68, 69, 71, 72, 73, 74, 75, 79, 80, 81, and 82 are rejected under 35 U.S.C. 102(a) as being anticipated by Expression Linked Polymorphism Database, profile for gene CDC14A, 2003 in view of Chenchik et al. (US 5,994,076).

The teachings of the Expression Linked Polymorphism Database are provided previously in this office action. These do not provide a method wherein the expression of CDC14A is detected by a step of producing an amplification product using primers pscific only for RNA encoded by said gene and/or for cDNA complementary to RNA encoded by said gene.

However, at the time the invention was made, it was known to use gene specific primers to produce amplification products prior to hybridization with predefined arrays, as taught by Chenchik et al. (throughout; Col. 11).

It would have been prima facie obvious to one of ordinary skill in the art to have modified the invention taught by Cocks et al. so as to have used gene specific primers to amplify target sequences prior to hybridization with a microarray. In this case, all of the claimed elements were known in the prior art and one skilled in the art could have combined the known elements as claimed to provide a predictable result, namely the production of probe hybridization molecules particularly amplified to hybridize to the array taught by Cocks et al.

Furthermore, regarding claims 74 and 81, at the time the invention was made, quantifying expression using PCR was routinely practiced. Given the disclosure that CDC14A was detected as expressed in the blood, it would have been obvious to one of ordinary skill in the art to have

used any routine means available to quantify expression of this gene in the blood, including quantitative PCR.

Claims 61, 62, 63, 67, 68, 69, 71, 72, 73, 74, 75, 79, 80, 81, and 82 are included in this 103 to address the embodiment wherein they depend from claim 59.

18. Claims 58, 59, 60, 61, 62, 63, 65, 67, 68, 69, 70, 71, 72, 73, 75, 76, 77, 78, 79, 80, 82, 83, 84, 85, 86, and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dutra et al. (Scand. J. Immunol. 45, 74-80, 1997) in view of both Affymetrix GeneChip Human Genome U133 Set datasheet, 2001 and Sharma et al. (WO 98/49342; cited in IDS).

Dutra et al. teach a method for detecting the expression of genes in a sample from individuals having Chagas disease and healthy controls which includes isolating RNA from blood samples, processing it, hybridizing it to a microarray, quantifying the expression and identifying differentially expressed genes. Maas et al. detected genes which were differentially expressed between patients having Chagas disease and healthy control patients, and classify gene expression as being with the patients who have the disease or healthy controls based on the level of difference of expression observed between the two types of samples.

Dutra et al. do not teach methods which screen for a differential gene expression in a wide variety of different genes, and namely do not detect CDC14A.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely,

Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Sharma et al. teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5). Sharma et al. specifically suggest that this method can be applied to the study of changes cause in the blood by the presence of a wide variety of diseases, including infectious diseases (p 5-6). Sharma et al. expressly teach that marker genes may be identified by differential hybridization methods, but do not exemplify a method which uses differential hybridization.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Dutra et al. so as to have additionally tested the blood, including total blood RNA as exemplified by Sharma et al. of the patients having Chagas disease and the healthy control samples for differential expression of a wide variety of genes, as directed by Sharma et al. One would have been so motivated by the express teachings of Sharma et al. that disease exerts a global effect on individuals and that this

effect can be measured by gene expression in the blood. The identification of markers for disease in the blood suggests a potential minimally invasive method to detect this disorder.

Dutra et al. in view of Sharma et al. do not specifically teach the use of a method which would have included using gene specific probes for CDC14A.

However, at the time the invention was made, Affymetrix had provided the GeneChip Human Genome U133 Set which included CDC14A among the genes which are detected by the array, and methods for using the array for the detection of differentially expressed genes in samples. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression, and at the time the invention was made it was routine to detect gene expression relative to a housekeeping gene. It would have been prima facie obvious to one of ordinary skill in the art to have detected differential expression in the methods taught by Dutra et al. in view of Sharma et al. with the Affymetrix gene. Because Affymetrix teaches arrays that are useful for detecting gene expression in a wide variety of genes, with the Affymetrix array providing means to detect over 38,000 transcripts, it would have been obvious to one of ordinary skill in the art to have substituted microarray detection methods for those exemplified by Sharma et al. to achieve the predictable result of detecting the expression of many different genes in the blood of individuals having Chagas disease versus controls. Such a substitution would have inherently and necessarily resulted in the detection and quantification of CDC14A in the blood samples of the patients having Chagas disease and the healthy control patients. One would have been motivated to continue to use the microarray analysis taught by the Affymetrix product sheet since the use of the microarray enables large scale screening of many different human genes, and Sharma et al. expressly teach that marker genes may be identified by differential hybridization

methods, which Heller et al. in view of the Affymetrix product sheet use (see Sharma, paragraph bridging pages 4-5).

At the time the invention was made, in differential expression assays using microarrays, expression statistical significance indicating a difference between two expression levels was commonly met if the p value was 0.05 or lower. Under this assumption, the values set forth in the claims, if observed would when practicing the method taught by Dutra et al. in view of Affymetrix and Sharma would have been be considered to indicate differentially expressed genes by one of ordinary skill in the art at the time the invention was made. Furthermore, at the time the invention was made, it was routine to consider a variety of different observed fold changes as relevant, and this was a variable that was optimized according to the assay and the practitioner's preferences, and the observation of significant probabilities.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

April 22, 2008